Remarks

Applicants respectfully request reconsideration of this application in view of the above amendments and the following remarks.

1. Status of the Claims

Claims 1-40 are pending in this application of which Claim 12-19 and 27-40 are withdrawn from consideration. Claims 38-40 have been canceled and withdrawn claims 14 and 37 have been amended in this response. Upon entry of these amendments, Claims 1-37 remain pending in this application.

2. Summary of the Amendments

Claims 14 and 37 have been amended to recite the steroid compounds disclosed at page 15, lines 27-30 of the specification.

No new matter has been added. Entry of the above amendments is respectfully requested.

3. Rejection of Claims 1-11 and 20-26 under 35 U.S.C. §103(a)

Claims 1-11 and 20-26 were rejected under 35 U.S.C. §103(a) as being unpatentable over Moran et al. (US 6,576,793 B1). Applicants respectfully traverse the rejection.

The Examiner alleges that "crystalline form is no more than a different physical form of the compound, and a mere different physical nature of the compound is unpatentable, absent evidence to the contrary" (Office Action, page 2, lines 18-20). The Examiner cited *Ex parte Hartop* 139 USPQ 525 and *In re Cofer 148* USPQ 268. as the authority for his position.

Applicants respectfully submit the Examiner has improperly applied the cited case law in this instance. As described in MPEP §2144.04 (VII.), the decision of *In re Cofer* actually supports a position opposite to that of the Examiner, namely *In re Cofer* found that claims to a crystalline form of a compound are patentable over a prior disclosure of the same compound. MPEP §2144.04 (VII.) specifically advises:

> Factors to be considered in determining whether a purified form of an old product is obvious over the prior art include whether the claimed chemical compound or composition has the same utility as closely related materials in the prior art, and whether the prior art suggests the particular form or structure of the claimed material or suitable methods of obtaining that form or structure. *In re Cofer*, 354 F.2d 664, 148 USPQ 268 (CCPA 1966) (Claims to the free-flowing crystalline form of a compound were held unobvious over references disclosing the viscous liquid form of the same compound because the prior art of record did not suggest the claimed compound in crystalline form or how to obtain such crystals.) (emphasis added)

The concept that a reference on which an obviousness rejection is based must provide an enabling disclosure has been articulated repeatedly in the case law. See, for example, *In re Payne*, 606 F.2d 303, 203 USPQ 245, 255 (CCPA 1979):

> References relied upon to support a rejection under 35 USC 103 must provide an enabling disclosure, i.e. they must place the claimed invention in the possession of the public. *In re Brown*, 51 CCPA 1254, 1259, 329 F.2d 1006, 1011, 141 USPQ 245, 249 (1964)

and, similarly, *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547, 1551 13 USPQ2d 1301, 1304:

> References relied upon to support a rejection for obviousness must provide an enabling disclosure. That is to say, they must place the claimed invention in the possession of the public.

to name only a few.

In the present instance, Claim 1 recites "crystalline *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)-phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride." (emphasis added)

In contrast, Moran '793 in Example 12, discloses a synthetic route to prepare a free base racemic form of the compound of Applicants' Claim 1. Nowhere does Moran '793 even suggest a specific salt of the disclosed compound or any compound in crystalline form. Consequently Moran '793 does not disclose a process for preparing any crystalline salt of the compound of Example 12. As described in the present specification at page 6, line 27, to page 7, line 21 and in the Examples, particular process steps are followed to obtain the presently claimed crystalline form. Such steps are neither disclosed nor implied in the cited reference. Accordingly, Moran '793 fails to provide an enabling disclosure of the crystalline dihydrochloride salt of Applicants' Claim 1 and thus

does not meet the requirements articulated in *In re Cofer* for a reference to support an obviousness rejection.

Furthermore, based on Moran '793, it is not possible to meet the three criteria for establishing a *prima facie* case of obviousness: a suggestion to modify the reference, a reasonable expectation of success, and the requirement that the reference teach or suggest all the claim limitations. As described above, the reference provides no suggestion to prepare the specific crystalline compound of Applicants' claims. As it provides no such suggestion, there can be no expectation of success. Adding to the lack of expectation of success, it is known that preparation of crystalline salt forms is not routine. Numerous patents describing the necessary processes to prepare specific crystalline salts of pharmaceutical agents attest to this fact. Third, the reference does not teach or suggest the claim limitations that the compound be crystalline and that it be in the form of a dihydrochloride salt. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness based on Moran '793.

For these reasons alone, independent Claim 1 is patentable over Moran '793. For the same reasons, independent Claim 7, which includes the subject matter of Claim 1 and an additional limitation, and Claims 2-6 and 8-11 dependent from Claim 1 are patentable over Moran '793.

Claims 2-7 recite specific characteristics of the crystalline dihydrochloride salt of Claim 1. Since the reference does not suggest the claimed compound in crystalline form nor how to obtain such crystals, it certainly does not suggest a crystalline compound with the specific x-ray powder diffraction pattern recited in Claims 2-4 and 7, the infrared absorption spectrum of Claim 5, nor the differential scanning calorimetry characteristic of Claim 6. For these additional reasons as well, Claims 2-7 are patentable over Moran '793.

Additionally, in assessing obviousness, objective evidence or secondary considerations such as unexpected results must be considered in every case in which they are present. (MPEP §2141 (III.) Applicants' specification provides evidence of the particular advantages of the presently claimed material for the preparation of pharmaceutical formulations for administration by inhalation. At page 6, lines 15-26, the specification discloses the present crystalline diHCl salt was stable upon exposure to elevated temperature and humidity. The chemical purity was unchanged after storage for

6 months at 40 °C and 75 % humidity. In addition, the material can be provided as particles in the size range appropriate for administration by inhalation. Consideration of this evidence of unexpected results, further supports the patentability of Claims 1-11.

Claims 20-26 recite a pharmaceutical composition comprising *N*-{2-[4-((*R*)-2-hydroxy-2-phenylethylamino)phenyl]ethyl}-(*R*)-2-hydroxy-2-(3-formamido-4-hydroxyphenyl)ethylamine dihydrochloride; a buffering agent; and water; wherein the buffering agent is present in an amount sufficient to provide the composition with a pH in the range of between about 4 and about 6. Analogously to the description above for Claims 1-11, Moran '793 does not teach or suggest a pharmaceutical composition with the limitations of Claim 20 and claims dependent therefrom. The reference, therefore, does not provide an enabling disclosure nor a reasonable expectation of success. Accordingly, the Examiner has failed to establish a *prima facie* case of obviousness for Claims 20-26 based on Moran '793.

Furthermore, the specification provides objective evidence of the unexpected benefits of a pharmaceutical composition according to Claims 20-26. At page 9, lines 9-16, the specification discloses that a pharmaceutical composition of the present invention was essentially unchanged after storage for nine months at 5 °C. In contrast, U.S. 6,040,344 identified stability of a pharmaceutical composition of formoterol tartrate, a different β_2 adrenergic receptor agonist, prepared for the same form of administration as a limitation to its acceptability. Consideration of the present evidence of unexpected results, further supports the patentability of Claims 20-26.

In summary, Claims 1-11 and 20-26 have been shown to be unobvious and patentable over Moran '793. Accordingly, the present rejection of Claims 1-11 and 20-26 under 35 U.S.C. §103(a) may be withdrawn.

4. Conclusion

In view of the foregoing, Applicants respectfully submit Claims 1-11 and 20-26 are in condition for allowance. Further, upon allowance, according to *In re Ochiai* (71F. 3d 1565, 37 USPQ2d 1127 (Fed. Cir. 1995) and MPEP §821.04, the restriction between Group I and Groups III (Claims 15-19) and V (Claims 28-30), both of which are process claims, and between Group I and Group VI (Claims 31-37), which are method of use claims, may be withdrawn. Reconsideration of this application is respectfully requested. Should there be any issues regarding this application that may be resolved by telephone, the examiner is invited to telephone the undersigned agent for Applicants at (650) 808-3764 (direct).

Respectfully submitted,
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